Journal of Traumatic Stress, Vol. 20, No. 5, October 2007, pp. 763–774 (© 2007)

Brain, Skull, and Cerebrospinal Fluid Volumes in Adult Posttraumatic Stress Disorder

Steven H. Woodward
National Center for PTSD, Clinical Laboratory and Education Division and Psychology Service, VA Palo Alto Healthcare System, Palo Alto, CA

Danny G. Kaloupek
National Center for PTSD, Behavioral Science Division, VA Boston Healthcare System, Boston and Division of Psychiatry, Boston University School of Medicine, Boston, MA

Chris C. Streeter
Division of Psychiatry, Boston University School of Medicine, Boston, MA

Matthew O. Kimble
Department of Psychology, Middlebury College, Middlebury, VT

Allan L. Reiss
Department of Psychiatry and Behavioral Sciences, Stanford University Medical School, Stanford, CA

Stephan Eliez
Department of Psychiatry, University of Geneva, Geneva, Switzerland

Lawrence L. Wald
Department of Radiology, Massachusetts General Hospital, Charlestown, and Department of Radiology, Harvard Medical School, Boston, MA

Perry F. Renshaw
Brain Imaging Center, McLean Hospital, Belmont, MA

Blaise B. Frederick
Department of Psychiatry, Harvard Medical School, Boston, and Brain Imaging Center, McLean Hospital, Belmont, MA

Major funding for this work was provided under a VA/DoD assistance agreement to Drs. Woodward and Kaloupek from the U.S. Army Medical Research and Material Command (DoD) administered through the Institute for Medical Research (VA). Special thanks are due to Stephen Grate and Lori Moll who facilitated the necessary arrangements at those institutions. Support was also provided by a National Institute on Alcohol Abuse and Alcoholism award (K23AA13149) and a VA Career Development Award to Dr. Streeter. The authors wish to thank the Research Services of the VA Palo Alto and VA Boston Healthcare Systems for their support. Institutional and technical support was also provided by the following individuals: At the VA Palo Alto HCS, John E. Drace, Patricia Spezia, Carla Ambriz, and Gary E. Gold, at the VA Boston HCS, Kelly Teresi, Frederick Kanter, Steven Blank, Susan Proctor, and Erica Stone; at Stanford University, Thomas J. Brosnan, Anil Patwardhan, and Eric Schmitt; at McLean Hospital, Rosemond Villafuerte, Ann Smith, and Eileen Connolly; and at the Defense Manpower Database Command, Micheal A. Dove. The authors are also grateful for the guidance provided by Kelvin O. Lim, Wendy R. Kates, Stephen E. Lindley, Danny H. Mathalon, Gregory A. Miller, Daniel W. King, Robert Rosenheck, Brian White, and H. Stefan Bracha.

Correspondence concerning this article should be addressed to: Steven H. Woodward, National Center for PTSD, Clinical Laboratory and Education Division, Mail Code 334 PTSD VA Palo Alto HCS, 795 Willow Rd., Menlo Park, CA 94025. E-mail: Steve.woodward@med.va.gov.

 DOI: 10.1002/jts.20241

Barton Lane
Department of Radiology, Stanford University Medical School, Stanford, CA

Javaid I. Sheikh
Department of Psychiatry and Behavioral Sciences, Stanford University Medical School, Stanford, CA

Wendy K. Stegman
National Center for PTSD, Clinical Laboratory and Education Division and Research Service, VA Palo Alto Healthcare System, Palo Alto, CA

Catherine J. Kutter
Psychology Service, White River Junction Veterans Affairs Medical Center, White River Junction, VT

Lorraine P. Stewart
Department of Psychology, University of Oregon, Eugene, OR

Rebecca S. Prestel
National Center for PTSD, Behavioral Science Division, VA Boston Healthcare System, Boston, MA

Ned J. Arsenault
National Center for PTSD, Clinical Laboratory and Education Division and Psychology Service, VA Palo Alto Healthcare System, Palo Alto, CA

Children and adolescents with maltreatment-related posttraumatic stress disorder (PTSD) exhibit smaller intracranial tissue volume than controls. Linear relationships have also been observed between intracranial tissue volume and the age of maltreatment onset. The authors explored associations among adult PTSD, early trauma, and cerebral volumes in 99 combat veterans. A bone-based estimate of cranial volume was developed to adjust for variation in body size. Posttraumatic stress disorder was not associated with smaller cerebral tissue volume, but rather with smaller cerebrospinal fluid (CSF) and cranial volumes. These findings co-occurred with expected effects of alcoholism and aging on cerebral tissue and CSF volumes. The results point to early developmental divergences between groups with and without PTSD following adult trauma.

Studies employing structural magnetic resonance imaging (MRI) have found that maltreated children with posttraumatic stress disorder (PTSD) have smaller intracranial volumes than controls (Carrion et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002). Although genetic contributions to smaller cerebral volumes are recognized (Gilbertson et al., 2002; Tramo et al., 1998), environmental influences may provide a more parsimonious explanation of the observed correlations between intracranial volume and age at maltreatment onset (see also Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002). Among studies reporting smaller hippocampal volume in adult PTSD, trends toward smaller cerebral tissue volumes are noted (c.f. Bremner et al., 2003; c.f. Gurvits et al., 1996; Lindauer et al., 2004; Woodward et al., 2006), although only one study has found a significant effect (Wignall et al., 2004). Childhood adversity may be a necessary condition for smaller brain volume in adult PTSD, but it is

only one of a number of risk factors (Brewin, Andrews, & Valentine, 2000). Hence, its impact in such studies may be diluted. In this study, relations between cerebral volumes and age at first trauma were investigated using a correlational approach. The effect of covarying for intelligence, also moderately correlated with brain volume (McDaniel, 2005) and a factor in PTSD risk (McNally & Shin, 1995), was also examined.

Although most PTSD neuroimaging studies have used cerebral macrovolumes to increase power in analyses of hippocampus and anterior cingulate cortex, they have not included methods of adjustment for normative variation in body size applicable to those macrovolumes, themselves. One approach is to covary for stature. After doing so, Fennema-Notestine et al. (2002) observed that victims of interpersonal violence had smaller intracranial volume than controls whether or not they met criteria for PTSD. A more proximate index might be supplied by an MRI-derived, bone-based estimate of cranial volume. We chose a bone-based estimate because skull-stripping performed on the T1-weighted images in preparation for brain tissue analyses typically removes meningeal tissue and nonsulcal cerebrospinal fluid (CSF), leaving approximately 6% of intracranial volume unaccounted for (Courchesne et al., 2000). Below, this bone-based estimate is referred to as *cranial volume*. *Cerebral volume* refers to total supratentorial brain tissue, alone. *Intracranial volume* commonly refers to the sum of brain tissue and CSF volumes, a variable that will not be considered here.

This study also examined sulcal and ventricular CSF volumes, expecting to find an increased volume in PTSD in agreement with two prior studies (Gurvits et al., 1996; Villarreal et al., 2002). Both alcoholism and normal aging are known to be associated with larger CSF volumes as well as smaller cerebral tissue volumes (reviewed in Pfefferbaum et al., 1992). Posttraumatic stress disorder was crossed with lifetime alcoholism and theater of service (Vietnam vs. Persian Gulf, hereafter labeled *cohort*), employing the latter factor as a proxy for aging. In this manner, this study sought to examine the independent and joint influences of PTSD in combination with known associates of adult cerebral structural variation.

METHOD

Participants were recruited through in-person contacts, flyers, and radio advertisements, participant databases, and referrals from clinicians and participants. All PTSD-positive (PTSD+) participants were treatment seeking. Although members of all subgroups were recruited at both sites, a majority of the Vietnam-era PSTD+ participants were tested at the Palo Alto site, whereas a majority of the Gulf War PTSD+ participants were tested at the Boston site. Hence, the Vietnam cohort was biased towards inpatients, and the Gulf War cohort towards outpatients. Initial screening established that all participants were combat-exposed U.S. military veterans of the Vietnam Conflict or the Gulf War reporting no current or past central nervous system (CNS) disease, no psychosis, and no alcohol or substance abuse/dependence in the last 6 months. Participants provided written informed consent in accordance with procedures of applicable Institutional Review Boards. Completing participants were paid $100. Participants meeting screening criteria were administered the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1997) and selected Axis I modules of the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995). Self-report instruments included the Combat Exposure Scale (CES; Keane et al., 1989), the Life Events Checklist (LEC; Blake et al., 2000), the Mississippi Scale for Combat-related PTSD (MISS; Keane, Caddell, & Taylor, 1988), the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the Michigan Alcohol Screening Test–Short Form (SMAST; Selzer, 1971). The MISS and CAPS item data were each missing for one participant and BDI data for two. Eighty-seven participants also underwent a structured interview developed for this study to determine (a) which LEC endorsements fulfilled PTSD Criterion A, and (b) at what age they occurred. (The time required to develop this measure mandated that testing begin before it was completed.)

Participants were excluded as follows: negative for current military PTSD and positive for lifetime civilian PTSD (18), currently alcohol/drug abusing/dependent

(14), probable brain damage/psychosis (8). Withdrawals were as follows: fatigue or nicotine withdrawal (4) and claustrophobia (5). Two participants missed scanning appointments and were thereafter unreachable. Eleven participants were excluded due to imaging artifact and two due to undiagnosed brain injury. The final sample included 99 military veterans. The PTSD+ participants met criteria for current PTSD as a result of experiencing one or more military traumas. PTSD-negative (PTSD−) participants were free of diagnosable PTSD, current or lifetime. Participants positive for alcohol abuse/dependence (ETOH+) were classified based upon meeting lifetime, but not current, criteria on the SCID. Psychotropic medications were continued during participation in this study. Seventy-nine percent of the PTSD+ participants were taking some form of psychotropic medication versus 21% of PTSD− participants. The PTSD+ versus PTSD− group medication rates by class were as follows: antidepressants, 61% versus 6%; selective serotonin reuptake inhibitors, 28% versus 2%; and anticonvulsant/mood-stabilizing medications, 26% versus 2%.

Magnetic resonance imaging was performed using two 1.5 T General Electric Signa systems (General Electric Corp., Fairfield, CT), one at the Diagnostic Radiology Center of Veterans Affairs Palo Alto Health Care System (Palo Alto, CA), and one at the Brain Imaging Center of McLean Hospital (Belmont, MA). The present data were derived from 124-slice T1-weighted volumetric spoiled gradient recalled (SPGR) image series (TR = 35 ms, TE = 6 ms, flip angle = 45 degrees, field of view = 24 cm, number of excitations = 1, image matrix size = 256 × 192). The raw data were imported into BrainImage (BrainImage 5.x, A. L. Reiss, Stanford University, Stanford, CA) for image optimizations that included correction for inhomogeneity artifact, resampling to cubic .9375 mm^3 voxels, positional normalization by reference to the anterior and posterior commissures and the intrahemispheric fissure, skull-stripping, tissue segmentation based upon a constrained fuzzy algorithm (Reiss et al., 1998), and parcellation according to a modified Talairach grid (Kates et al., 1999; Talairach & Tournoux, 1988).

Using positionally normalized images, cranial volume was estimated by summing three rectangular volumes determined by the cross-sectional areas of the cranial vault at anterior, central, and posterior slices, each multiplied by 33% of cranial length (See Figure 1). As reliable discrimination of the inner table of the skull from underlying CSF is difficult on T1-weighted images, the boundary between the outer table of the skull and overlying muscle was employed. Ventral landmarks and the locations of width vectors were based upon features of cerebral tissue. The central slice was established 10 slices (9.375 mm)

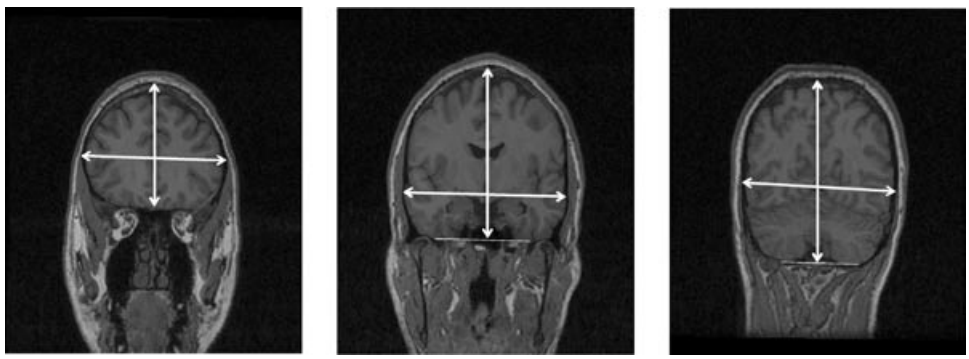

Figure 1. Estimation of cranial volume was based upon the total anteroposterior (AP) distance between frontal and occipital poles of the brain along the axis determined by the anterior-commissure–posterior-commissure (AC-PC) line, and three equally weighted rectangular estimates of cranial cross-sectional area, an anterior cross-section at 25% of AP distance, a posterior cross-section at 75% of the AP distance, and a medial cross-section at 10-mm posterior to the AC. (See text for further details).

posterior to the anterior commissure. The height of the vault at this slice was measured on a line following the central sulcus, terminating dorsally at the external skull boundary, and ventrally at a line tangent to the inferior margins of the temporal lobes, bilaterally. The width of the cranium at this slice was estimated using a line intersecting the superior margin of the nadir of the "U" formed by the first decussation of white matter from the temporal isthmus, bilaterally, and terminating at the external skull boundaries. The first and last slices containing brain defined total cranial length. The anterior slice was identified at 25% of this distance and the posterior slice at 75%. The height of the anterior slice was measured as the length of the line following the central sulcus, terminating dorsally at the external skull boundary and ventrally at the planum sphenoidale. The width at the anterior slice was measured on the line connecting the superior margins of the insertions of the masseter muscles, bilaterally. Height at the posterior slice was estimated as the length of the line following the central sulcus, terminating dorsally at the external skull boundary, and ventrally at the intersection with a line tangent to the inferior margins of the cerebellar hemispheres. Width at the posterior slice was measured as the length of the line tangent to the superior margin of the cerebellar vermis and terminating at the external skull boundaries. The imputed volume enclosed and so over-estimated the ellipsoid cranial volume.

Intrarater and cross-site reliability estimates for cranial volume, cerebral tissue volume, sulcal CSF volume, and ventricular volume ranged from $r_{icc} = .94$–$.99$, reflecting the use of nearly identical MRI systems and exclusive reliance upon unsegmented tissue volumes. As no site differences were detected, the two subsamples were aggregated into a single sample of 99 participants. Group differences were tested with univariate ANOVA and ANCOVA crossing PTSD, cohort, and ETOH. Covariates used were cranial volume, height, and Wechsler Adult Intelligence Scale (WAIS) (Psychological Corporation, New York, NY) vocabulary subscale score. Effects were also retested after excluding women. Effect sizes are expressed as partial eta-squared (η_p^2), interpretable as the proportion of variance accounted for by an effect in the context of multiple between-group factors. Selected linear relationships between cerebral macrovolumes and continuous psychometric indices were investigated.

RESULTS

The PTSD+ participants exhibited expected elevations in the prevalence of current and past major depressive disorder (MDD) along with higher BDI scores (see Tables 1 and 2). Posttraumatic stress disorder was also associated with lower WAIS vocabulary scores (particularly among PTSD+/ETOH+ participants), and with experiencing a first Criterion A event at an earlier age. Posttraumatic stress disorder was not associated with alcoholism due to oversampling of PTSD+/ETOH− participants, although even among ETOH− participants, PTSD was associated with more abuse behaviors as indicated by higher SMAST scores. ETOH+ participants were approximately 2 years older than ETOH− participants, and reported slightly earlier Criterion A events and MISS scores. The Vietnam cohort reported higher combat exposure, higher MISS scores, a higher rate of MDD, and was slightly taller than the Gulf War cohort.

Cerebral Tissue Volume

Cerebral volume estimates are presented in Table 3. Cerebral tissue volume was smaller in PTSD+ participants; however, as in most earlier studies, this result was not statistically significant, $F(1,91) = 2.73$, $p = .10$; $\eta_p^2 = .03$. Consistent with the alcohol literature, cerebral tissue volume was significantly smaller in ETOH+ participants, $F(1,91) = 6.57$, $p < .05$; $\eta_p^2 = .07$. There was no effect of cohort on cerebral tissue volume, $F < 1$, $\eta_p^2 = .01$.

After adjustment for cranial volume, PTSD+ participants unexpectedly exhibited larger cerebral tissue volume than PTSD− participants, $F(1,90) = 5.41$, $p < .05$; $\eta_p^2 = .06$). Adjustment for cranial volume also modified the effects of ETOH and cohort, rendering the former insignificant, $F(1,90) = 1.99$, *ns*, $\eta_p^2 = .02$, and latter significant (Gulf War > Vietnam), $F(1,90) = 14.62$, $p < .001$, $\eta_p^2 = .14$. We believe these observations are best

Table 1. Sample Characteristics: Means and Standard Deviations of Continuous Variables

	Vietnam cohort				Gulf War cohort							
	PTSD+ ($n = 38$)		PTSD− ($n = 25$)		PTSD+ ($n = 13$)		PTSD− ($n = 23$)		Effect sizes (partial η^2)			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	PTSD	Cohort	ETOH	Interactions
Age	53.5	2.6	56	3.5	37	5.7	36.7	3.9	.018	.862	.011	PTSD x COHORT: .052; PTSD x COHORT x ETOH .113
Years of education	14.4	1.8	15.5	2.2	14.3	1.7	15.0	1.9	.079	.009	.012	ns
WAIS vocabulary subscale score	47.4	12.0	55.5	7.1	45.6	12.4	52.5	8.0	.128	.015	.030	PTSD x ETOH: .050
Combat Exposure Scale	29.8	9.9	24.2	8.2	19.9	11.8	8.6	6.0	.164	.300	.003	COHORT x ETOH: .045
CAPS-TS	75.9	18.4	8.8	9.0	75.9	19.9	8.4	11.0	.815	.000	.004	*ns*
MISS	122.8	18.8	68.2	15.8	107.8	15.8	59.0	11.1	.704	.110	.047	*ns*
BDI	25.0	8.9	4.6	3.7	21.0	7.3	4.3	4.0	.631	.027	.029	*ns*
SMAST	3.9	4.0	2.1	3.8	3.3	3.6	0.5	0.9	.161	.048	.363	PTSD x ETOH: .067
Age at ETOH onset	24.6	8.0	21.5	8.7	26.7	5.0	22.1	5.9	.060	.007		*ns*
Age at first Criterion A event	12.4	6.2	19.3	6.7	11.1	6.9	17.0	8.4	.172	.027	.052	*ns*
Height	70.2	2.6	70.9	2.7	69.0	3.3	69.4	3.5	.009	.050	.015	*ns*

Note. Tabulation of continuous demographic, diagnostic, and psychometric data by posttraumatic stress disorder (PTSD) diagnosis and cohort. Sizes of main effects associated with the grouping factors, expressed as partial $\eta 2$, are located in columns headed PTSD, cohort, and ETOH respectively. Column labeled Interactions lists any interactions. ETOH = Alcohol Abuse/Dependence; CAPS-TS = Clinician-Administered PTSD Scale total severity score; MISS = Mississippi Scale Score; BDI = Beck Depression Inventory; SMAST = Michigan Alcohol Screening Test–Short Form; *ns* = nonsignificant.

understood in light of main effects on cranial volume reported below. No effects on cerebral tissue volume were modified by adjustment for WAIS vocabulary score, height, or the exclusion of female participants.

Sulcal and Ventricular Cerebrospinal Fluid Volumes

Sulcal CSF volume exhibited a significant three-way interaction of PTSD, cohort, and ETOH, $F(1,91) = 4.53$, $p < .05$, $\eta_p^2 = .05$. After decomposing this interaction, it was observed that the associations of PTSD and ETOH with sulcal CSF volume differed over cohorts. Vietnam cohort members exhibited a PTSD × ETOH interaction, $F(1,59) = 4.26$, $p < .05$, $\eta_p^2 = .07$, wherein PTSD was associated with substantially smaller sulcal CSF volume in ETOH− participants, $F(1,33) = 10.17$, $p < .01$, $\eta_p^2 = .24$, but not in ETOH+ participants, $F(1,27) < 1$, $\eta_p^2 = .007$. The Gulf War cohort exhibited only a main effect in which PTSD was again associated with smaller CSF volume, $F(1,32) = 8.32$, $p < .01$, $\eta_p^2 = .21$. The main effect of PTSD on sulcal CSF volume was significant as well, $F(1,91) = 9.41$, $p < .01$, $\eta_p^2 = .09$.

Table 2. Sample Characteristics: Percentages of Categorical Variables

	Vietnam cohort		Gulf War cohort		Effects		
	PTSD+ %	PTSD− %	PTSD+ %	PTSD− %	PTSD	cohort	ETOH
Male	100.0	100.0	77.0 (10)	83.0 (19)	*ns*	$X^2(1) = 13.18^{***}$	*ns*
Caucasian	65.8	92.0	53.8	69.6	$X^2(1) = 4.17^{*}$	*ns*	$X^2(1) = 4.18^{*}$
Current MDD	78.9	4.0	69.2	4.3	$X^2(1) = 53.27^{***}$	$X^2(1) = 4.34^{*}$	*ns*
Lifetime MDD	89.5	28.0	76.9	17.4	$X^2(1) = 40.20^{***}$	$X^2(1) = 6.36^{*}$	*ns*
Lifetime ETOH	44.7	44.0	46.2	39.1	*ns*	*ns*	
Criterion A event before age 8	41.0	4.0	30.0	14.0	$X^2(1) = 10.48^{***}$	*ns*	*ns*
Criterion A event before age 18	69.0	26.0	90.0	41.0	$X^2(1) = 8.67^{**}$	*ns*	*ns*

Note. Tabulation of categorical demographic, diagnostic, and psychometric data by posttraumatic stress disorder (PTSD) diagnosis and cohort. X^2s associated with the grouping factors are indicated in columns headed PTSD, cohort, and ETOH, respectively. MDD = Major Depressive Disorder; ETOH = Alcohol Abuse/Dependence; *ns* = nonsignificant.
$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Table 3. Cerebral Volumes

	Vietnam cohort								Gulf War cohort							
	PTSD+				PTSD−				PTSD+				PTSD−			
	ETOH+		ETOH−		ETOH+		ETOH−		ETOH+		ETOH−		ETOH+		ETOH−	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Cerebral tissue	1086	61	1092	105	1097	95	1118	82	983	84	1136	70	1094	89	1113	95
Sulcal CSF	166	38	138	20	163	20	164	29	109	28	102	13	143	36	117	15
Ventricular CSF	27	11	22	8	28	12	24	10	17	5	13	2	23	15	14	7
Cranial	2666	153	2609	209	2732	190	2762	148	2288	201	2598	160	2604	168	2659	190

Note. Means and standard deviations of subgroup volumes of cerebral tissue, sulcal cerebrospinal fluid (CSF), ventricular CSF, and supratentorial cranium expressed in milliliters.

Sulcal CSF volume was larger in the older Vietnam cohort, $F(1,91) = 45.94$, $p < .001$, $\eta_p^2 = .34$, and in ETOH+ participants, $F(1,91) = 6.21$, $p < .05$, $\eta_p^2 = .06$. Ventricular CSF volume exhibited a pattern similar to sulcal CSF, larger in both the Vietnam cohort, $F(1,91) = 15.3$, $p < .001$, $\eta_p^2 = .14$, and in ETOH+ participants, $F(1,91) = 6.70$, $p < .05$, $\eta_p^2 = .07$; however, the association with PTSD was reduced to a trend, $F(1,91) = 1.66$, *ns*, $\eta_p^2 = .02$; PTSD+: 19.5 mL; PTSD−: 22.3 mL.

Adjustment for cranial volume left the main effects of cohort and ETOH on both sulcal and ventricular CSF volumes essentially unchanged; however, the previously strong main effect of PTSD on sulcal CSF volume was reduced to a trend, $F(1,90) = 3.58$, *ns*, $\eta_p^2 = .04$. No effects on sulcal or ventricular CSF volume were modified by adjustment for height, WAIS vocabulary, or both, or by the exclusion of female participants.

Cranial Volume

Although originally estimated solely to increase power in analyses of cerebral tissue and CSF, cranial volume exhibited multiple between-groups effects, including a three-way interaction of PTSD, cohort, and ETOH, $F(1,91) = 4.82$, $p < .05$, $\eta_p^2 = .05$. In decomposing this

interaction, it was observed that in the Vietnam cohort, cranial volume was associated with a main effect of PTSD only, $F(1,59) = 5.66$, $p < .05$, $\eta_p^2 = .03$, and was smaller in PTSD+ participants. In the Gulf War cohort, both PTSD, $F(1,32) = 8.77$, $p < .01$, $\eta_p^2 = .22$, and ETOH, $F(1,32) = 8.26$, $p < .01$, $\eta_p^2 = .21$, were associated with smaller cranial volume. Cranial volume was also associated with a significant two-way interaction of ETOH and cohort such that within the Gulf War cohort, ETOH+ participants had smaller cranial volume, $F(1,34) = 5.40$, $p < .05$, $\eta_p^2 = .14$, whereas in the Vietnam cohort they did not, $F < 1$, $\eta_p^2 = .003$. Finally, simple main effects on cranial volume were all significant. Smaller cranial volume was associated with PTSD, $F(1,91) = 14.54$, $p < .001$; $\eta_p^2 = .14$, ETOH, $F(1,91) = 4.71$, $p < .05$, $\eta_p^2 = .05$, and Gulf War cohort membership, $F(1,91) = 15.78$, $p < .001$, $\eta_p^2 = .15$. These effects were not modified by adjustment for height, WAIS vocabulary, or the exclusion of female participants.

Linear Relationships

Among the cerebral macrovolumes measured in this sample, only cranial volume exhibited significant linear correlations with psychiatric severity measures. In all cases, these were inverse, CAPS-TS: $r(97) = -.21$, $p < .05$; MISS: $r(96) = -.21$, $p < .05$; BDI: $r(95) = -.23$, $p < .05$, and were strengthened after cranial volume was residualized against height, CAPS-TS: $r(97) = -.22$, $p < .05$; MISS: $r(96) = -.32$, $p < .01$; BDI: $r(95) = -.32$, $p < .01$. As cranial volume was correlated with WAIS vocabulary score, $r(97) = .21$, $p < .05$, which in turn was correlated with severity indices, CAPS-TS: $r(97) = -.39$, $p < .001$; MISS: $r(96) = -.39$, $p < .001$; BDI: $r(95) = -.33$, $p < .001$, relations between severity indices and cranial volume were retested after partialing out shared variance with WAIS vocabulary score. With one exception, these relationships remained significant, CAPS-TS: $r(96) = -.17$, *ns*; MISS: $r(96) = -.27$, $p < .01$; BDI: $r(94) = -.28$, $p < .01$.

Only cranial volume was nominally correlated with age at first Criterion A-qualifying traumatic event, $r(85) = .21$, $p = .05$. To further assess this relationship, the sample was split into participants whose first traumas occurred prior to age 8 ($n = 20$, PTSD+/PTSD−: 16/4, mean age at first trauma = 5.3 years) versus age 8 or later ($n = 67$, PTSD+/PTSD−: 26/41, mean age at first trauma = 18.2 years). This cut-point was chosen because it was within the asymptotic phase of cranial development and classified enough cases into the smaller subsample ($n = 20$) for reliable correlations. In participants with trauma prior to age 8, age at first trauma exhibited a significant positive rank-order correlation with cranial volume, $\rho(18) = .62$, $p < .01$ (see Figure 2), which persisted when one or both variables were residualized against height. In participants reporting first trauma at age 8 or later, age at first trauma was uncorrelated with cranial or cerebral tissue volume (rs = −.09 to .07). The above pattern persisted when the cut-point was reduced to 7 or 6.

DISCUSSION

Adults with combat-related PTSD exhibited sulcal CSF and cranial volumes smaller than those of traumatized controls, whereas cerebral tissue volume exhibited only a trend in the same direction. The most familiar ground for evaluating unexpected features of these results is provided by sulcal CSF volume. Cerebrospinal fluid is well discriminated in T1-weighted scans, and its volume has been analyzed in many neuroimaging studies of alcoholism and aging (e.g., Pfefferbaum et al., 1992). Significantly, in this sample of combat veterans, the association of PTSD with smaller sulcal CSF volume co-occurred with larger CSF volumes in alcoholic participants and members of the older Vietnam cohort. It is reasonable to posit that the former association emerged here only because other important sources of variance in CSF volume were accounted for. Although earlier studies have reported larger CSF volumes in PTSD, a history of alcoholism was confounded with PTSD in those samples. It is noteworthy that lifetime alcoholic Vietnam cohort members did not exhibit smaller sulcal CSF volume in association with PTSD even though concurrent effects of alcoholism and aging (via cohort) were presumably accounted for. As discussed below, the cohort factor clearly

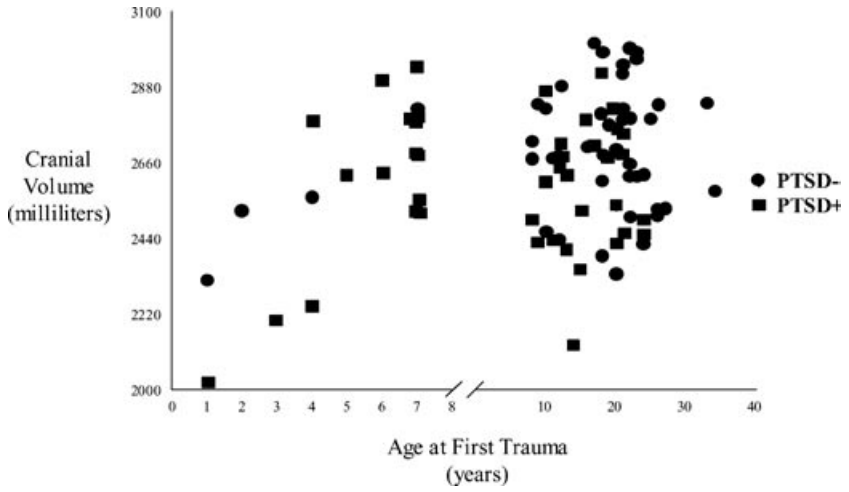

Figure 2. A scatterplot of cranial volume by age at first trauma for participants experiencing that trauma at age 7 or younger (left panel) versus age 8 or older (right panel). Posttraumatic stress disorder-positive (PTSD+) cases are plotted with squares, PTSD− cases with circles. Note the strong relationship between age at first trauma and cranial volume in the early traumatized group, and the absence of such a relationship in the later traumatized group.

incorporates variance beyond that associated with normal aging.

Although equally unexpected, the finding of smaller adult cranial volume in PTSD is strongly reminiscent of the observations of De Bellis, especially in the observed inverse correlation between a summary cerebral volume and an index of early trauma. The difference between the two sets of observations could be bridged by an analysis of cranial volumes in the samples of De Bellis and Carrion. Although PTSD was confounded with both MDD and psychotropic medication, available data do not suggest either could account for the observed associations between PTSD and smaller cranial and sulcal CSF volumes. Indeed, MDD appears to be moderately associated with increased CSF volume (Elkis, Friedman, Wise, & Meltzer, 1995).

The observed group differences in cranial volume are almost certainly too small to directly impact brain function. Instead, they may have implications for the timing of emergence of PTSD risk. Because cranial growth is asymptotic by age 5 (Courchesne et al., 2000), differences between groups with and without PTSD must reflect a developmental divergence that long predates adult trauma. It remains to be determined whether this divergence can best be accounted for by genes, environment, or gene-environment interactions. As noted earlier, many cerebral features are inherited (Tramo et al., 1998); however, there are also indications that development of the human craniofacial skeleton is highly sensitive to environmental conditions. Among neonates, smaller external head circumference is associated with adverse prenatal environments, and is seen in those born of mothers with poor health (e.g., Thame, Wilks, McFarlane-Anderson, Bennett, & Forrester, 1997) and low socioeconomic status (SES; e.g., Hoey & Cox, 1990). Postnatally, head circumference is associated with poor nutrition (Ivanovic et al., 2004), and it is plausible that early childhood trauma co-occurs with neglect extending to a failure to meet the nutritional requirements for normal cranial growth. A large body of data also supports the impact of early developmental adversity on hypothalamic–pituitary–adrenal (HPA) axis dysregulation and later mood disorder (Nemeroff & Vale, 2005). The present findings may suggest that adversity-driven basal cortisol elevation interferes with bone formation in the developing cranium. The HPA-axis is stress-reactive from

infancy (Gunnar, 1992), and many forms of adversity, including maternal stress (Essex, Klein, Cho, & Kalin, 2002), depression (Halligan, Herbert, Goodyer, & Murray, 2004), and low SES (Lupien, King, Meaney, & McEwen, 2000), are associated with basal cortisol elevations in young children. Bone formation zones express glucocorticoid (GRα) receptors; (Abu, Horner, Kusec, Triffitt, & Compston, 2000), and elevated circulating glucocorticoid hormones suppress bone formation and skeletal growth in infancy (Yeh et al., 2004). Prenatally, maternal ingestion of glucocorticoid drugs, as well as maternal psychological stress, are associated with smaller neonatal head circumference (Thorp, Jones, Knox, & Clark, 2002). Such a mechanism need not result in smaller adult stature, or smaller total cerebral tissue volume because the long bones and brain continue to grow into the second decade and so can manifest "catch-up" growth denied the skull (Simon, Fernando, Czernichow, & Prieur, 2002). A combination of twin and longitudinal studies will be necessary to resolve these questions.

Results obtained from the Gulf War cohort suggest that early childhood differences in cranial volume may distinguish alcoholic from nonalcoholic trauma survivors before addictive behavior is manifested or alcohol toxicity can impact the brain; however, the Vietnam cohort did not exhibit this association. The strong, nonaging-related cohort differences to be discussed below complicate the interpretation of this difference. To our knowledge, only one prior study has examined cranial volume in alcoholics, finding no difference from controls; however, this study used a spherical estimate based upon a single linear measurement (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995). In addition, PTSD was not accounted for. As early childhood adversity contributes to adult alcoholism (Dube, Anda, Felitti, Edwards, & Croft, 2002), its contribution to cerebral structural correlates of adult alcoholism may warrant further investigation.

The observation of smaller cranial volume in Gulf War than in Vietnam veterans demonstrates unequivocally that the cohort factor, notwithstanding its aging-like associations with CSF volumes, incorporates nonaging variance. It is well known that different recruitment methods led to the formation of the Vietnam and Gulf War forces. Conscripted personnel accounted for approximately 30% of U.S. combat deaths during the Vietnam War, whereas the all-volunteer force deployed to the Persian Gulf was composed of persons electing military service. Could biases introduced by self-selection for military service in the Gulf War cohort have been sufficiently strong to produce differences in cranial volume, and if so, by what mechanism? To date, most comparisons of U.S. military recruits to the general population have focused on differences in SES, which appear small (Booth & Schmiegel, 1998). In contrast, preliminary studies have suggested that rates of childhood adversity in recent military samples range from 30% to 50%, with men reporting more physical and women more sexual abuse (Merrill et al., 1998; Rosen & Martin, 1996). According to the National Comorbidity Study (Kessler et al., 1994), the prevalence of physical abuse in the general population is 3% to 5%. If voluntary enlistment in the military is associated with elevated rates of childhood adversity, it is conversely plausible that conscription produced a force with rates closer to that of the general population. Germane to this argument, Gulf War veterans have exhibited sharply higher cohort-controlled rates of homelessness than have Vietnam veterans (Rosenheck, Frisman, & Chung, 1994), a finding commensurate with relatively higher rates of childhood adversity (Herman, Susser, Struening, & Link, 1997). In sum, there exist data compatible with the possibility that the Vietnam and Gulf War cohorts, like PTSD+ versus PTSD− participants, are characterized by differences in their early developmental environments that may have neurobehavioral consequences. In this sample, only trends toward earlier trauma in the Gulf War cohort were observed; nevertheless, the large cranial volume differences suggest the inclusion of early neurodevelopmental measures in future investigations of military recruitment methods and resulting forces may be warranted.

REFERENCES

Abu, E. O., Horner, A., Kusec, V., Triffitt, J. T., & Compston, J. E. (2000). The localization of the functional glucocorticoid receptor

alpha in human bone. Journal of Clinical Endocrinology and Metabolism, 85, 883–889.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. Archives of General Psychiatry, 4, 561–571.

Blake, D., Weathers, F., Nagy, L., Kaloupek, D., Klauminzer, G., Charney, D., et al. (2000). Clinician-Administered PTSD Scale (CAPS) instructional manual. Boston: National Center for PTSD.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Charney, D. S., & Keane, T. M. (1997). Clinician-Administered PTSD Scale for DSM-IV: Current and lifetime version. Boston: Behavioral Science Division, Boston VA Medical Center/Neurosciences Division; West Haven, CT: West Haven VA Medical Center.

Booth, S., & Schmiegel, K. (1998). Socioeconomic status and performance in the US Army and US Marine Corps. Monterey, CA: Naval Postgraduate School.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., et al. (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. American Journal of Psychiatry, 160, 924–932.

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. Journal of Consulting and Clinical Psychology, 68, 748–766.

Carrion, V. G., Weems, C. F., Eliez, S., Patwardhan, A., Brown, W., Ray, R. D., et al. (2001). Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biological Psychiatry, 50, 943–951.

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., et al. (2000). Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology, 216, 672–682.

De Bellis, M. D., Keshavan, M. S., Clark, D. B., Casey, B. J., Giedd, J. N., Boring, A. M., et al. (1999). A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. Biological Psychiatry, 45, 1271–1284.

De Bellis, M. D., Keshavan, M. S., Shifflett, H., Iyengar, S., Beers, S. R., Hall, J., et al. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. Biological Psychiatry, 52, 1066–1078.

Dube, S. R., Anda, R. F., Felitti, V. J., Edwards, V. J., & Croft, J. B. (2002). Adverse childhood experiences and personal alcohol abuse as an adult. Addictive Behaviors, 27, 713–725.

Elkis, H., Friedman, L., Wise, A., & Meltzer, H. Y. (1995). Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. Archives of General Psychiatry, 52, 735–746.

Essex, M. J., Klein, M. H., Cho, E., & Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. Biological Psychiatry, 52, 776–784.

Fennema-Notestine, C., Stein, M. B., Kennedy, C. M., Archibald, S. L., & Jernigan, T. L. (2002). Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. Biological Psychiatry, 52, 1089–1101.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). Structured Clinical Interview for the DSM-IV Axis-I Disorders. New York: Biometrics Research Department, New York State Psychiatric Institute.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature Neuroscience, 5, 1242–1247.

Gunnar, M. R. (1992). Reactivity of the hypothalamic–pituitary–adrenocortical system to stressors in normal infants and children. Pediatrics, 90, 491–497.

Gurvits, T. V., Shenton, M. E., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W., et al. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biological Psychiatry, 40, 1091–1099.

Halligan, S. L., Herbert, J., Goodyer, I. M., & Murray, L. (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. Biological Psychiatry, 55, 376–381.

Herman, D. B., Susser, E. S., Struening, E. L., & Link, B. L. (1997). Adverse childhood experiences: Are they risk factors for adult homelessness? American Journal of Public Health, 87, 249–255.

Hoey, H. M., & Cox, L. A. (1990). Head circumference standards for Irish children. Acta Paediatrica Scandinavica, 79, 162–167.

Ivanovic, D. M., Leiva, B. P., Perez, H. T., Olivares, M. G., Diaz, N. S., Urrutia, M. S., et al. (2004). Head size and intelligence, learning, nutritional status and brain development. Head, IQ, learning, nutrition and brain. Neuropsychologia, 42, 1118–1131.

Kates, W. R., Warsofsky, I. S., Patwardhan, A., Abrams, M. T., Liu, A. M., Naidu, S., et al. (1999). Automated Talairach

atlas-based parcellation and measurement of cerebral lobes in children. Psychiatry Research, 91, 11–30.

Keane, T. M., Caddell, J. M., & Taylor, K. L. (1988). Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: Three studies in reliability and validity. Journal of Consulting and Clinical Psychology, 56, 85–90.

Keane, T. M., Fairbank, J. A., Caddell, J. M., Zimering, R. T., Taylor, K. L., & Mora, C. A. (1989). Clinical evaluation of a measure to assess combat exposure. Psychological Assessment, 1, 53–55.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Archives of General Psychiatry, 51, 8–19.

Lindauer, R. J., Vlieger, E. J., Jalink, M., Olff, M., Carlier, I. V., Majoie, C. B., et al. (2004). Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. Biological Psychiatry, 56, 356–363.

Lupien, S. J., King, S., Meaney, M. J., & McEwen, B. S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. Biological Psychiatry, 48, 976–980.

McDaniel, M. A. (2005). Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. Intelligence, 33, 449–458.

McNally, R. J., & Shin, L. M. (1995). Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam Combat veterans. American Journal of Psychiatry, 152, 936–938.

Merrill, L. L., Newell, C. E., Milner, J. S., Koss, M. P., Hervig, L. K., Gold, S. R., et al. (1998). Prevalence of premilitary adult sexual victimization and aggression in a Navy recruit sample. Military Medicine, 163, 209–212.

Nemeroff, C. B., & Vale, W. W. (2005). The neurobiology of depression: Inroads to treatment and new drug discovery. Journal of Clinical Psychiatry, 66(Suppl 7), 5–13.

Pfefferbaum, A., Lim, K. O., Zipursky, R. B., Mathalon, D. H., Rosenbloom, M. J., Lane, B., et al. (1992). Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: A quantitative MRI study. Alcoholism, Clinical and Experimental Research, 16, 1078–1089.

Reiss, A. L., Hennessey, J. G., Rubin, M., Beach, L., Abrams, M. T., Warsofsky, I. S., et al. (1998). Reliability and validity of an algorithm for fuzzy tissue segmentation of MRI. Journal of Computer Assisted Tomography, 22, 471–479.

Rosen, L. N., & Martin, L. (1996). The measurement of childhood trauma among male and female soldiers in the U.S. Army. Military Medicine, 161, 342–345.

Rosenheck, R., Frisman, L., & Chung, A. M. (1994). The proportion of veterans among homeless men. American Journal of Public Health, 84, 466–469.

Selzer, M. L. (1971). The Michigan alcoholism screening test: The quest for a new diagnostic instrument. American Journal of Psychiatry, 127, 1653–1658.

Simon, D., Fernando, C., Czernichow, P., & Prieur, A. M. (2002). Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. Journal of Rheumatology, 29, 1296–1300.

Sullivan, E. V., Marsh, L., Mathalon, D. H., Lim, K. O., & Pfefferbaum, A. (1995). Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. Alcoholism, Clinical and Experimental Research, 19, 110–122.

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical.

Thame, M., Wilks, R. J., McFarlane-Anderson, N., Bennett, F. I., & Forrester, T. E. (1997). Relationship between maternal nutritional status and infant's weight and body proportions at birth. European Journal of Clinical Nutrition, 51, 134–138.

Thorp, J. A., Jones, P. G., Knox, E., & Clark, R. H. (2002). Does antenatal corticosteroid therapy affect birth weight and head circumference? Obstetrics and Gynecology, 99, 101–108.

Tramo, M., Loftus, W., Stukel, T., Green, R., Weave, R. J., & Gazzaniga, M. (1998). Brain size, head size, and intelligence quotient in monozygotic twins. Neurology, 50, 1246–1252.

Villarreal, G., Hamilton, D. A., Petropoulos, H., Driscoll, I., Rowland, L. M., Griego, J. A., et al. (2002). Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biological Psychiatry, 52, 119–125.

Wignall, E. L., Dickson, J. M., Vaughan, P., Farrow, T. F., Wilkinson, I. D., Hunter, M. D., et al. (2004). Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. Biological Psychiatry, 56, 832–836.

Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Kimble, M. O., Reiss, A. L., Eliez, S., et al. (2006). Hippocampal volume, posttraumatic stress disorder, and alcoholism. American Journal of Psychiatry, 163, 674–681.

Yeh, T. F., Lin, Y. J., Lin, H. C., Haung, C. C., Hsieh, W. S., Lin, C. H., et al. (2004). Outcomes at school age after postnatal dexamethosone therapy for lung disease of prematurity. New England Journal of Medicine, 350, 1304–1313.